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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
GUSSOW, ANNE	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,445	NORDSTEDT ET AL.	
	Examiner	Art Unit	
	Anne M. Gussow	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11,20,21,28-33,37-55 and 59-69* is/are pending in the application.

4a) Of the above claim(s) *2,3,5-9,33,42-50,61-67 and 69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,11,20,21,28-32,37-41,51-55,59,60 and 68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/15/06, 7/14/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-9, 11, 20-21, 28-33, 37-55, 59-60, and 68, and the species of SEQ ID Nos. 24, 25, 26, 33, 34, and 35 in the reply filed on October 30, 2007 is acknowledged. The traversal is on the ground(s) that the inventions listed as Groups I-V relate to a single general inventive concept. This is not found persuasive because in a national stage entry application, applicant is entitled to a single product, a method of making the product, and a single method of using the product. The application claims three separate products, an antibody, a nucleic acid, and a virus, and three separate methods of using the antibody, a method of treating (which was included in Group I), a method of diagnosing an amyloid disorder, and a method of detecting ApoE-CTD.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 2, 3, 5-9, 33, 42-50, 61-67, and 69 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 30, 2007.

3. Claims 1, 4, 11, 20, 21, 28-32, 37-41, 51-55, 59, 60, and 68 are under examination.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on May 15, 2006 and July 14, 2006 have been fully considered by the examiner and an initialed copy of the IDS is included with the mailing of this Office Action.

Specification

5. The disclosure is objected to because of the following informalities: in the brief description of the figures there is no description of the parts of figure 1 (A and B) and figure 9 (A through D).

Appropriate correction is required.

6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

7. Claims 4 and 37-41 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Applicant has elected the CDR species of SEQ ID Nos. 24-26 for the heavy chain and SEQ ID Nos. 33-35 for the light chain. Only these six sequences have been searched. For the purposes of this office action the limitations of the CDRs have been read into claim 1. It is not clear how the sequences in claims 4 and 37-41 further limit the sequences in the previous claims.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 54 and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 54 recites a humanized antibody of claim 1. Claim 1 recites a human antibody. It is not clear how a human antibody can be humanized.

Claim 55 recites a chimeric antibody of claim 1. Claim 1 recites a human antibody. It is not clear how a human antibody could be a chimeric.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1, 4, 11, 20, 21, 28-32, 37-41, 51-55, 59, 60, and 68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a human antibody or antibody fragment which binds to the C-terminal domain of ApoE and comprises either a heavy chain and a light chain or three CDRs of the heavy chain and three CDRs of the light chain, does not reasonably provide enablement for an antibody comprising fewer than six CDRs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or used the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

> Wands states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims recite a human antibody or antibody fragment, which antibody or fragment: (i) binds to a polypeptide having the amino acid sequence shown in SEQ ID NO: 1 of the C-terminal domain of Apolipoprotein E (ApoE-CTD) or the amino acid sequence of a part thereof; and (ii) (a) binds to human plaques; (b) comprises a heavy chain CDR3 region comprising the sequence shown in SEQ ID No. 26 and/or binds to said polypeptide in the presence of very low density lipoprotein (VLUL).

The specification discloses an antibody that binds to the C-terminal domain of Apolipoprotein E (Apo E). The specification discloses the antibody comprises a heavy chain and a light chain with three CDRs in the heavy chain and three CDRs in the light chain. The specification does not disclose an antibody having only a single CDR, or fewer than six CDRs.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proceedings of the National Academy of Sciences, 1982. Vol. 79, page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. MacCallum et al. (Journal of Molecular Biology, 1996. Vol. 262, pages 732-

745) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right column) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left column). Pascalis et al. (Journal of Immunology, 2002. Vol. 169, pages 3076-3084) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right column). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left column).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site is underscored by Casset et al. (Biochemical and Biophysical Research Communications, 2003. Vol. 307, pages 198-205), which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al. also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left column) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left column). Vajdos et al. (Journal of Molecular Biology, 2002. Vol. 320, pages 415-428) additionally state that antigen binding is primarily mediated by

the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left column). Holm et al (Molecular Immunology, 2007. Vol. 44, pages 1075-1084) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract). Chen et al. (Journal of Molecular Biology, 1999. Vol. 293, pages 865-881) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866). Wu et al. (Journal of Molecular Biology, 1999. Vol. 294, pages 151-162) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left column) but certain residues have been identified as important for maintaining conformation.

There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability to produce an antibody consisting of fewer than six CDRs. The specification does not teach how to produce an antibody with fewer than six CDRs.

In view of the lack of predictability of the art to which the invention pertains, undue experimentation would be required to produce the claimed antibody with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively produce the claimed antibody and absent

working examples providing evidence which is reasonably predictive that the claimed antibody would be effective consisting of fewer than six CDRs, commensurate in scope with the claimed invention.

12. Claim 60 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim recites a method of treating a subject suffering from an amyloid disorder comprising administering to said subject a therapeutically effective amount of an antibody of antibody fragment that binds to the C-terminal domain of Apo E.

The specification discloses a mouse model of Alzheimer's disease in which the presence of ApoE in brain plaques can be detected with an antibody that binds to the C-terminal domain of Apo E. The specification does not disclose whether the binding of the antibody results in the removal of existing plaques or the inhibition of formation of new plaques. The specification does not disclose models or examples of other amyloid disorders.

It is well known in the art that the treatment of Alzheimer's disease is unpredictable. Huang, et al (US PAT 6,787,519, issued September 7, 2004) teach post mortem immunostaining of mouse brain sections for C-terminal truncated forms of Apo E (example 2, column 40). Huang, et al. teach that C-terminal truncated forms of Apo E are present to a greater extent in Alzheimer's disease brains than in normal brains

(column 38-39). Cordell, et al. teach in vitro methods of reducing the amount of Apo E produced in glial cells by administering compounds such as inhibitors of HMG CoA, cholesterol biosynthesis; protein isoprenylation, or NF-κB activation that reduce the amount of Apo E present in tissue culture samples (examples 5-8). Cordell, et al. do not teach in vivo administration of compounds to reduce the amount of Apo E.

There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability to treat an amyloid disorder with an antibody that binds to the C-terminal domain of Apo E. The specification does not disclose the effect on plaques of binding an antibody to the C-terminal domain of Apo E. The specification does not disclose the therapeutic effect of treatment with an antibody that binds to the C-terminal domain of Apo E.

Claim Rejections - 35 USC § 101

13. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

14. Claims 1, 4, 11, 20, 21, 28-32, 37-41, 51-55, and 59 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1, 4, 11, 20, 21, 28-32, 37-41, 51-55, and 59, as written, do not sufficiently distinguish over antibodies as they exists naturally because claims 1, 4, 11, 20, 21, 28-32, 37-41, 51-55, and 59 do not particularly point out any non-naturally

occurring differences between the claimed antibodies and binding compositions and the structure of naturally occurring antibodies

In the absence of the hand of man, the naturally occurring antibodies are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1966)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F.Supp 68 (1967), 155 USPQ 139, (District Court, New Jersey, 1967)). Amendment of the claims to recite "an isolated" or "purified" antibody or similar language would obviate this rejection.

Conclusion

15. No claims are allowed.

16. Claims 1, 4, 11, 20, 21, 28-32, 37-41, 51-55, 59, 60, and 68 are free of the prior art. The closest prior art is Huang (US PG PUB 2004/0157267, filed July 24, 2003).

Huang teaches a method for diagnosing Alzheimer's disease in a subject by detecting carboxyl-terminal truncated forms of Apo E. Huang does not teach nor reasonably suggest an antibody that binds to the C-terminal domain of Apo E or a method for treating Alzheimer's disease with an antibody that binds to the C-terminal domain of Apo E.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne M. Gussow whose telephone number is (571) 272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow

January 2, 2008

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER